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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/694,383	KANDIMALLA ET AL.	
	Examiner	Art Unit	
	MICHELLE HORNING	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14-19,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *15-17 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14,18,39 and 40* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is responsive to communication filed 6/10/2010.

Claims 12, 14, 18, 39 and 40 are under current examination. Note that claim18 has been rejoined in view of the applied prior art.

Any rejection(s) and/or objection(s) not reiterated herein have been withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/10/2010 has been entered.

Claim Objections

Claim 12 is objected to because of the following informalities: for the improper use of the following phrase, "each X independently is independently selected from". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 14, 18, 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The

claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to (in part) an immunostimulatory oligonucleotide compound comprising the formula:

5'-Um…U1-X1-X2-Y-Z-X3-X4-D1…Dm-3' (see claim 12) or 5'-Um…U3-U2-U1-X1-X2-Y-Z-X3-X4-D1-D2-D3…Dm-3' (see claim 14), wherein

Y is a non-natural pyrimidine nucleoside;

And, Z is a non-natural purine nucleoside.

The following quotation from section 2163 of the MPEP is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed or through disclosure of a functional characteristic of the claimed genus coupled with a

known or disclosed non-functional characteristic (structure) that correlates to the function.

As noted above, Y and Z of the sequence formulas are defined as a non-natural pyrimidine nucleoside or a non-natural purine nucleoside. As claimed, Y and Z may be any modified purine or pyrimidine (e.g. a modified uridine, a modified adenosine, a caffeine molecule, uric acid, etc.).

While the claims are broad in view of a compound's structure, functionally the claims are limited to a compound that is *immunostimulatory*. The instant specification provides evidence that some replacements of the deoxynucleosides (e.g. 2'-methylribonucleosides) in a CpG motif can suppress immunostimulatory activity because such a modification does not allow for the proper recognition and/or interaction of the CpG-motif with the proteins required in the immunostimulatory pathway (p. 4, lines 5+). The instant specification further discloses that the precise structural requirements and specific functional groups of the CpG motif necessary for the recognition of protein/receptor factor that is responsible for immune stimulation have not yet been studied in detail (p. 4, lines 23+). Note that different functional effects would be expected for different structures and the different structures of an immunostimulatory compound comprising, for example, a non-natural purine nucleoside (Z) would be endless in structural possibilities. It is not clear from the instant specification what specific structures are required in order to retain the recognition and/or interaction with the proteins that are responsible for immune stimulation, as described by the instant specification. Given no structure to function correlation is provided, the functional effects

of a sequence comprising any non-natural pryimidine or purine in a CpG motif is unpredictable.

Given the breath of the claims and the lack of structure to function correlations of an immunostimulatory compound comprising any non-natural pryimidine or purine, the claims are rejected for lacking written description support. The dependent claims fall herein.

Claim Rejections - 35 USC § 102-MAINTAINED

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Cook (US Patent No. 5599797-previously cited) as further evidenced by the instant specification and Stein and Cheng (*Science*, 1993-previously cited). This rejection is extended to claim 18. Applicant's arguments are addressed below.

The claims are drawn to (in part): an immunostimulatory oligonucleotide compound comprising as sequence of formula 5'-Um…U1-X1-X2-Y-Z-X3-X4-D1…Dm-3' wherein:

Y is a non-natural pyrimidine nucleoside;

Z is a non-natural purine nucleoside;

each X is a 1',2' dideoxyribose;

each U is an immunostimulatory moiety;

each D is an immunostimulatory moiety;

m represents a number from 0 to 30; and,

wherein at least one X, U or D is a 1',2'-dideoxyribose.

Cook discloses phosphorothioate oligonucleotide sequences joined together by *all* phosphorothioate linkages (see abstract, SEQ ID NO: 1). The phosphorothioate oligonucleotide CCTTTCGCGACCACACTA (SEQ ID NO: 1, col. 12, lines 55+) is an immunostimulatory oligonucleotide compound comprising a sequence formula of 5'-Um…U1-X1-X2-Y-Z-X3-X4-D1…Dm-3', wherein Y is a non-natural pyrimidine nucleoside (see underlined C in SEQ ID NO: 1 above), Z is a non-natural purine nucleoside (see underlined G in SEQ ID NO: 1 above), and wherein at least one X, U or D is an immunostimulatory moiety and m is a number between 0 and 30.

It is noted here that Figure 3 of the instant specification provides the structure of 1',2'-dideoxyribose or a phosphorothioate linkage as shown in Figure 1 of the Stein and Cheng reference); see lines 9 and 18 of instant claim 12 and claim 18.

It is also noted that Cook describes oligonucleotides which comprises phosphorothioates as exhibiting resistance to nucleases and as generally more chemically stable than natural phosphodiester oligonucleotides (co. 2, lines 56+). Note that this meets the definition of an "immunostiumlatory moiety" as defined by the instant specification [0065]. The definition provides that an immunostimulatory moiety is a structure that causes the immunostimulatory oligonucleotide to be more immunostimulatory than it would be in the *absence* of the immunostimulatory moiety. The phosphorothioate-containing oligonucleotide is more immunostimulatory in that the

phosphorothioate would lead to a more stable structure allowing the oligonucleotide to perform its structure-dependent immunostimulatory function as opposed to one lacking the phophorothioate which would lead to nuclease-dependent degradation.

Claim 14 is rejected under 35 U.S.C. 102(b) as being anticipated by Weiner et al. (*PNAS*, 1997-previously cited) as further evidenced by the instant specification and Stein and Cheng (*Science*, 1993-previously cited). Applicant's arguments are addressed below.

Claim 14 is drawn to (in part): an immunostimulatory oligonucleotide compound comprising a sequence of formula:

5'……U3-U2-U1-X1-X2-Y-Z-X3-X4-D1-D2-D3…Dm-3'

wherein, Y is a non-natural pyrimidine nucleoside;

Z is a guanosine;

X1, X2, X3, X4, U1, U2, U3, Um, D1, D2, D3 and Dm are naturally occurring nucleoside,

provided that at least one of X1, X2, X3, X4, U1, U2, U3, D1, D2 or D3 is not a naturally-occurring nucleoside.

Weiner et al. discloses the immunostimulatory oligonucleotide TCTCCCAGCGTGCGCCAT which comprises 2 CpG motifs (ODN 1758, Table 1, p. 10834). This immunostimulatory oligonucleotide comprises the formula,

5'……U3-U2-U1-X1-X2-Y-Z-X3-X4-D1-D2-D3…Dm-3'

wherein Y is a non-natural pyrimidine nucleoside (see 1st CG above or CpG);

Z is a guanosine;

Wherein X3 and X4 are naturally occurring nucleosides (see TG);

Wherein D1 is a non-naturally occurring nucleoside (see 2nd CG above or CpG), meeting the claim limitations of at least one of X1, X2, X3, X4, U1, U2, U3, D1, D2 or D3 is not a naturally occurring nucleoside and D1 is a 1', 2'-dideoxyribose.

It is noted here that Figure 3 of the instant specification provides the structure of 1',2'-dideoxyribose or a phosphorothioate linkage as shown in Figure 1 of the Stein and Cheng reference).

Claim Rejections - 35 USC § 103-MAINTAINED

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cook (US Patent No. 5599797-previously cited) as further evidenced by the instant specification and Stein and Cheng (*Science*, 1993-previously cited). Applicant's arguments are addressed below.

As discussed above, the teachings by Cook discloses phosphorothioate oligonucleotide sequences joined together by *all* phosphorothioate linkages (see abstract, SEQ ID NO: 1). The phosphorothioate oligonucleotide CCTTTCGCGACCACACTA (SEQ ID NO: 1, col. 12, lines 55+) is an immunostimulatory oligonucleotide compound comprising a sequence formula of 5'-Um…U1-X1-X2-Y-Z-X3-X4-D1…Dm-3', wherein Y is a non-natural pyrimidine nucleoside (see underlined C in SEQ ID NO: 1 above), Z is a non-natural purine nucleoside (see underlined G in SEQ ID NO: 1 above), and wherein at least one X, U or D is an immunostimulatory moiety and m is a number between 0 and 30.

It is noted here that Figure 3 of the instant specification provides the structure of 1',2'-dideoxyribose or a phosphorothioate linkage as shown in Figure 1 of the Stein and Cheng reference).

Cook does not disclose a specific sequence comprising a 4-thiouracil.

Cook describes generally incorporating modified bases including a 4-thiouracil in the phosphorothioate oligonucleotides for the advantage of increasing their nuclease resistance in order to facilitate their use as therapeutic reagents (col. 7, lines 45+ and instant claim 39).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings by Cook and further incorporate a 4-thiouracil into the sequence CCTTTCGCGACCCACACTA (SEQ ID NO: 1). One of ordinary skill in the art at the time the invention was made would have been motivated to do so for the advantage of increasing its nuclease resistance and to facilitate its use as therapeutic reagents as taught by Cook. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success given the underlying techniques and methods are widely used and commonly known as shown by the applied prior art (e.g. modifying oligonucleotide sequences, etc.). The invention as a whole was *prima face* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 14 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiner et al. (*PNAS*, 1997-previously cited) in further view of Cook (US Patent No. 5599797-previously cited) as further evidenced by the instant specification and Stein and Cheng (*Science*, 1993-previously cited). Applicant's arguments are addressed below.

As discussed above, Weiner et al. discloses the immunostimulatory oligonucleotide TCTCCCAGCGTGCGCCAT which comprises 2 CpG motifs (ODN 1758, Table 1, p. 10834). This immunostimulatory oligonucleotide comprises the formula,

5'……U3-U2-U1-X1-X2-Y-Z-X3-X4-D1-D2-D3…Dm-3'

wherein Y is a non-natural pyrimidine nucleoside (see 1st CG above or CpG);

Z is a guanosine;

Wherein X3 and X4 are naturally occurring nucleosides (see TG);

Wherein D1 is a non-naturally occurring nucleoside (see 2nd CG above or CpG), meeting the claim limitation of at least one of X1, X2, X3, X4, U1, U2, U3, D1, D2 or D3 is not a naturally occurring nucleoside and D1 is a 1', 2'-dideoxyribose.

Weiner et al. does not disclose incorporating a 4-thiouracil in immunostimulatory oligonucleotides.

It is noted here that Figure 3 of the instant specification provides the structure of 1',2'-dideoxyribose or a phosphorothioate linkage as shown in Figure 1 of the Stein and Cheng reference).

Cook describes generally incorporating modified bases including a 4-thiouracil in the phosphorothioate oligonucleotides for the advantage of increasing their nuclease resistance in order to facilitate their use as therapeutic reagents (col. 7, lines 45+ and instant claim 39).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings by Weiner et al. and Cook and further incorporate a 4-thiouracil into the sequence TCTCCCAGCGTGCGCCAT (ODN 1758). One of ordinary skill in the art at the time the invention was made would have been motivated for the advantage of increasing its nuclease resistance and to facilitate its use as therapeutic reagents. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success given the underlying techniques and methods are widely used and commonly known as shown by the

applied prior art (e.g. modifying oligonucleotide sequences, etc.). The invention as a whole was *prima face* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed 6/10/2010 have been fully considered but they are not persuasive. Applicant's arguments note that claims 12 and 14 have been amended to remove the term "immunostimulatory moiety" and that neither Cook nor Weiner teach the recited elements at their respective positions.

This is not persuasive. See the maintained rejections above; Cook and Weiner teach immunostimulatory sequences which meet the claim limitations of claims 12 and 14.

Double Patenting-MAINTAINED

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 12, 14, 18, 39 and 40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 18 of copending Application No. 10/865245. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to an immunostimulatory oligonucleotide comprising a CpG as well as linkers. Note that both sets of claims are broad in scope in that they overlap in common structures.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 12, 14, 18, 39 and 40 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent

No. 7824696. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to an immunostimulatory oligonucleotide comprising a CpG and other non-naturally occurring nucleosides, including a C3-alkyl linker.

Claims 12, 14, 18, 39 and 40 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 7262286. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an immunostimulatory oligonucleotide containing a CpG formula and in which the C is an analog, including a 4-thiouracil. Because both sets are broad in scope, they are both drawn to similar sequence structures.

Response to Arguments

In response to the rejection(s), Applicant submits that the copending applications 10/865, 245 and 10/694, 418 (now US Patent 7824696) have later filing dates. This has been noted, however, until the rejection is properly addressed, the rejections are maintained on the record. Applicant further argues that the claims of Patent No. 7262286 do not teach any of the positional modifications of claims 12 and 14. This is incorrect as both sets of claims are drawn to a phosphorothioate or a 1', 2'-dideoxyribose (see Figure 3 of instant specification and Fig. 1 in the Stein and Cheng reference). Also note that claims 39 and 40 are drawn to a 4-thiouracil as required in the ‘286 patent.

Conclusion

No claim is allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE HORNING whose telephone number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ZACHARIAH LUCAS can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/M. H./
Examiner, Art Unit 1648

/Zachariah Lucas/
Supervisory Patent Examiner, Art Unit 1648